PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BRANTS, Johan, Philippe, Emi
De Clercq, Brants & Partners
E. Gevaertdreef 10a
B-9830 Sint-Martens-Latem
BELGIQUE

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	06.09.2004
Applicant's or agent's file reference ABL-015-PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 03/00194	07.11.2003	08.11.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/24

Applicant
ABLYNX N.V.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 08.03.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office - Gitschiner Str. 103
D-10958 Berlin
Tel. +49 30 25901 - 0
Fax: +49 30 25901 - 840

Authorized Officer
Alconada Rodríguez,

Formalities officer (incl. extension of time limits)
Geier, A
Telephone No. +49 30 25901-706

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-70 as originally filed

Claims, Numbers

1-49 as originally filed

Drawings, Sheets

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 22-24 (complete) and 25, 26 and 39 (in part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 22-24 (complete) and 25, 26 and 39 (in part)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	-
Inventive step (IS)	Claims	1-9,11-21, 25-49
Industrial applicability (IA)	Claims	-

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99/09055 A (INNOGENETICS NV ;SABLON ERWIN (BE); BUYSE MARIE ANGE (BE)) 25 February 1999 (1999-02-25)

D2: MUYLDERMANS S: "SINGLE DOMAIN CAMEL ANTIBODIES: CURRENT STATUS" REVIEWS IN MOLECULAR BIOTECHNOLOGY, ELSEVIER, AMSTERDAM,, NL, vol. 74, no. 4, June 2001 (2001-06), pages 277-302, XP001057480 ISSN: 1389-0352

D3: WO 90/10707 A (JONKER MARGREET ;MEIDE PETRUS HENDRIKUS V D (NL)) 20 September 1990 (1990-09-20)

D4: ELS CONRATH K ET AL: "Camel single-domain antibodies as modular building units in bispecific and bivalent antibody constructs" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 276, no. 10, 9 March 2001 (2001-03-09), pages 7346-7350, XP002248402 ISSN: 0021-9258

1 Document D1 provides antibodies and engineered antibody constructs, such as humanized single-chain Fv fragments, chimeric antibodies, diabodies, triabodies, tetravalent antibodies, peptabodies and hexabodies which can be used to treat diseases related to interferon-γ activity (see page 10, line 13 to page 11, line 27). Examples of such diseases are: septic shock, cachexia, multiple sclerosis and psoriasis (see page 12, lines 4-7). None of the antibodies provided in D1 can be considered as single domain antibodies, since thy all contain at least part of the VH and part of the VL chains and therefore, the subject-matter of claim 1 is new.

2 However, the subject-matter of claim 1 does not involve an inventive step. D1, which can be regarded as the closest prior art, provides different type of recombinant antibodies against IFN-γ. This document differs from the present application in that claim 1 relates to single-domain antibodies (i.e. they contain only the variable part of the heavy chain). The problem to be solved by the subject-matter of claim 1 can be summarised as the provision of alternative anti IFN-γ Antibodies. The skilled person would consider the use of the VHH antibodies as described in D2 as an obvious alternative to the recombinant antibodies of D1, in particular because D1 also mentions that anti-IFN-γ antibodies

can be obtained from ruminants, among others from llama (see page 24, lines 25-29). Therefore, no inventive step can be acknowledged for the subject-matter of the claims which relate to anti-IFN-γ single domain antibodies and the uses thereof (**claims 1-3, 11, 14-21, 25-49**). All reach-through claims which relate to methods to identify agents that modulate the binding of the IFN-γ to the IFN-γ antibodies or to IFN-γ receptor; use of the anti-IFN-γ Antibodies for the treatment or prevention of inflammatory reactions ; use of the anti-IFN-γ Antibodies for the purification of IFN-γ and methods for the recombinant production of anti-IFN-γ are obvious uses of anti-IFN Antibodies are either directly derivable from the prior art or fall within the usual practice and knowledge of the person of ordinary skills in the art and therefore, lack and inventive step and can only be allowed if they relate to new and inventive subject-matter.

3 An inventive step could be acknowledged for the whole application if restricted to those antibodies for which functional evidence is given that they provide an unexpected or surprising effect which could not be foreshadowed from the general obvious combination of D1 and D2. In particular, those anti-IFNγ VHHs identified in examples 10 and 14 and which are characterised by having an IC50 lower than that of a polyclonal IFNγ Antibodies in an assay that measures the ability of the antibodies to prevent binding of IFNγ to its receptor. The antibodies showing those properties are those identified in Tables 6 and 11 of the description and which correspond to those defined by SEQ ID NO:2, 4, 6, 8, 11, 13, 19, 20, 22, 24, 26-29 (monovalent VHHs) and 59-61 (bivalent VHHs).

4 The use of bifunctional VHH Antibodies comprising an anti-IFN-γ VHH and a second single domain antibody directed against a serum protein (**claims 4-7**) is rendered obvious by the combined teaching of D1 and D2. D1 teaches anti-IFN γ bivalent and bispecifc antibodies which, in addition to a variable domain specific for IFN-γ, could contain a second domain specific for another molecule, including some molecules found in serum like interleukins and TGF-beta (page 22, lines 12-20). Thus, the subject-matter of claim 4 differs from the teaching of D1 in that claim 4 relates to bispecific VHHs whereas D1 relates to diabodies having at least one VH and one VL domain. The skilled person would consider the information available in the prior art, in particular the teaching in D2 that two VHH antibodies of different specificities can be combined into a bispecific bivalent VHH diabody (see page 297, left-hand column, last paragraph to right-hand column, first paragraph and figure 6), and would attempt to construct bivalent bispecific

antibodies comprising an anti-IFNγ binding region and a second binding region against a serum protein, thus arriving in an obvious manner to the subject-matter of **claim 4**. **Claims 5-7** relate to particular embodiments of the bispecific single domain antibodies of claim 4 which, in the absence of any surprising or unexpected technical effect, can not be considered as involving an inventive step.

5 Other elements of the invention are also rendered obvious by the prior art. The combination of anti-IFN-γ and anti-TNF-alpha, either as bivalent Antibodies or as composition comprising both Antibodies is known from D3 which discloses a composition comprising an anti-IFN-γ Antibodies and an anti-TNF-alpha Antibodies and the use thereof for the treatment of immunoregulatory disorders. It would be obvious for the skilled person to prepare either bivalent VHH comprising an anti-IFN-γ and anti-TNF-alpha VHH or to prepare a composition comprising both VHH and thus, the subject-matter of **claims 8, 12 and 13** lacks an inventive step.

6 The bivalent VHH comprising at least two anti-IFN-γ VHH is also not inventive, since it is known from D2 and D4 that bivalent VHH containing two identical VHH domains can be obtained having more than one VHH with the same specificity and that these bivalent VHH show an increased avidity than the corresponding monovalent VHH (see page 297, left-hand column, last paragraph to right-hand column, first paragraph and figure 6 see page 297, left-hand column, last paragraph to right-hand column, first paragraph and figure 6 in D2 and age 7349, right-hand column, paragraphs 3-45 in D4). In addition, D1 also teaches diabodies having multiple IFN-γ binding domains. Therefore, it would be obvious for the skilled person to consider the use of camelidae VHHs as building blocks as in D2 and D4 for the constructions of bivalent anti-IFNγ antibodies according to D1, thus arriving to the subject-matter of **claims 9 and 10** which lack an inventive step.